

May 21, 2003

Lynne Jones  
Technical Contact  
The Synthetic Organic Chemical Manufacturers Association (SOCMA)  
Metal Carboxylates Coalition  
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Washington, DC 20036

Dear Ms. Jones:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Metal Carboxylates Category posted on the ChemRTK HPV Challenge Program Web site on January 23, 2003. I commend The Synthetic Organic Chemical Manufacturers Association (SOCMA) Metal Carboxylates Coalition for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that The Synthetic Organic Chemical Manufacturers Association (SOCMA) Metal Carboxylates Coalition advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at [tsca-hotline@epa.gov](mailto:tsca-hotline@epa.gov).

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director  
Risk Assessment Division

Enclosure

cc: A. Abramson  
W. Penberthy  
M. E. Weber

**EPA Comments on Chemical RTK HPV Challenge Submissions:  
Metal Carboxylates Category**

**Summary OF EPA Comments**

The sponsor, The Metal Carboxylates Coalition, submitted a test plan and robust summaries to EPA for the Metal Carboxylates Category dated December 20, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 23, 2003.

EPA believes that the category and test plan as proposed are not adequately supported. The submitter needs to provide a better basis for the category hypothesis that the toxicity of the category members can be deduced from testing performed on the acid portion and metal portion of each metal carboxylate rather than testing the metal carboxylate itself.

EPA's preliminary comments appear below. EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

**EPA Comments on the Metal Carboxylates Category Challenge Submission**

**Category Definition**

The Metal Carboxylate Category consists of 19 metal salts of carboxylic acids and one phenolic salt (Subcategory 5) divided into six subcategories based on the carbon number of the carboxylic acid.

**Category Justification and Test Plan**

*Testing Approach*

The approach used by the submitter essentially treats the carboxylate ion and metal ion of each category member independently, such that combining information from separate testing of the acid and metal corresponding to each metal carboxylate is argued to be equivalent to testing the metal carboxylate itself. The submitter provides test data for many of the acids and metals and testing is proposed for some of the members (Table 1 of the test plan).

The submitter bases this testing approach on the following "key points" (page 15 of the test plan):

- a common structure for the organic and metal ions
- complete dissociation of the member substances at environmental and physiological pH values
- "general" bioequivalency of the salts with the same metal ion
- similar use pattern

These "key points" are discussed below; however, the points are interrelated and the discussions overlap. Page and table numbers refer to the test plan.

(a) *A common structure for the organic portion and metal ion.* While 19 of 20 members have carboxylic acid structures, they differ in chain length and complexity. The submitter accommodates these differences by developing subcategories based on the carboxylate structure. The submitter specifically states that the subcategories do not reflect differences in the bioavailability of the metal ion, states that bioavailability differences are related (solely) to the dissociation constants as shown by the unpublished work of Stopford et al. (page 13; see section (b) below), and assumes that dissociation to the free metal ion and free acid

occurs rapidly. In addition, the submitter assumes that any metal in the undissociated form is unavailable. The submitter concludes that the toxicity of the metal carboxylate can be determined from the individual toxicities of the metal ion and the parent acid.

This view does not account for all of the possibilities available to these substances. For example, the submitter equates the presence of the free metal ion with bioavailability (see element “1” at the bottom of page 13), but does not discuss potential differences in the bioavailability of metal complexes formed to differing degrees with the different acids in the category. It is possible that soluble metal carboxylates will be transported significantly better than uncomplexed metal salts in biological systems. In addition, while the submitter uses pKa values to demonstrate the separation of the acid and metal ions into a water-solvated metal ion and (at lower pH) an organic acid, these values do not necessarily demonstrate formation of a free metal and free acid (see discussion under (b), below). This may be especially significant when considering a category so diverse in terms of both metal and organic ion. The submitter therefore needs to discuss these and other related issues associated with the potential differences among the subcategories.

*(b) Complete dissociation of the member substances at environmental and physiological pH values.* The submitter states that all members of the category become free metal ions and organic acids at environmental and physiological pH values. The submitter supports this by citing the unpublished work of Stopford et al. and the dissociation constants of the category members, stating that the data demonstrate that the toxicity and environmental behavior (including ecotoxicity, mammalian toxicity, and environmental fate and transport) of the metal ions and organic acids separately are equivalent to the toxicity and environmental behavior of the metal carboxylates. The work of Stopford et al. appears to be central to this concept, but the details of the experimental method are not presented in either the test plan or robust summaries and therefore no understanding of the applicability of these results to the availability of the metal ions and organic acids can be developed. Even without the experimental details, the results presented in Table 2 do not fully support the submitter’s conclusions of bioequivalency in that the “% of available metal” at pH 7.4 varies significantly with the matrix (i.e., intestinal, alveolar, or interstitial fluids). The importance or implications of these differences, including their relationship to toxicity, are not fully discussed in the test plan.

In addition, the submitter does not address other important concepts when considering the stability of metal-ligand pairs, including the stability constants and ligand exchange rates for these substances. The submitter’s presentation does not clearly describe the stability of metal-ligand complexes in this category. The test plan cites acid dissociation constants (pKa) for the metal carboxylates, but discusses metal-ligand dissociation. While pH will strongly affect the stability of the metal-ligand complex, the pKa of a metal complex refers to the acidity of a metal-bound water ligand, whereas the metal-ligand dissociation constant describes the tendency of the ligand to dissociate from the metal ion. Various equilibria in solution may include protonation and deprotonation of the ligand (acid) and of any metal-bound water ligands, as well as formation and dissociation of the metal-ligand complex. The pH will determine which species predominate (potentiometric titration can determine stability constants and predominant species for metal-ligand complexes). A discussion of this and similar information and why it supports the toxicological and environmental equivalency of the complex, free metal, and free acid is essential to supporting the premise.

*(c) “General” bioequivalency of the salts with the same metal ion.* The concepts in (a) and (b) above are essential to demonstrating the “general” bioequivalency for the salts of a given metal with different organic acids or with chloride. While such general bioequivalency may apply to the metals and metal carboxylates in this category, there was no supporting detailed analysis of comparative experimental evidence for one or more metal carboxylates and corresponding metal salt and organic acid. Where there may be multiple competing processes, theory alone is not sufficient to determine which will predominate, especially when the systems are as complex as physiological processes and environmental systems, and the substances are as varied as the members of this category. Some of the metals in question can be toxic if absorbed

(e.g. barium, cobalt). A small increase in absorption, for example, as a result of complexation with the rather lipophilic distearate, would result in a substantive change in both the dose-response relationship for these metals and in the environmental behavior of the carboxylate. Some case-specific demonstration of the concept is needed before generally applying it to all of the metal carboxylates of interest. In addition, the test plan needs to address how planned representative testing will be used to confirm the premise for each endpoint.

(d) *Similar use pattern.* The submitter describes the uses of the metal carboxylates in this category. These use patterns vary widely and suggest that there are significant chemical differences in the metal carboxylates that may also be reflected in their behavior in environmental and biological systems.

### **Test Plan**

For many substances it is unclear just how the submitter plans to use the existing data on specific metals and acids for each endpoint group to determine the toxicity of the individual metal carboxylates or subcategories.

The test plan indicates that chromosomal aberration testing is planned for cobalt neodecanoate; Table I implies that this will be an *in vivo* test, which is beyond the scope of the U.S. HPV Challenge Program. The plan included no rationale for conducting an *in vivo* study; the nature of the planned testing needs clarification.

The Table of Contents and the text refer to Matrices 1 to 6 for the individual subcategories, but these were not a part of the submission.

### **Specific Comments On Robust Summaries**

Each of the six robust summary sections for metal 2-ethylhexanoates includes the SIDS dossier for 2-ethylhexanoic acid to support the 'dissociation product' logic for those chemicals. In each case, the page numbering at SIDS dossier page 5 is reset to 1. This results in confusing and repeated page numbers until page 541, from which the remaining 274 pages are numbered consecutively. In addition, the 2-ethylhexanoic acid dossier on page 230 of the pdf file has one less page than the other five.

There were two robust summary sections for copper naphthenate because that chemical was used to support conclusions for both zinc and cobalt salts of naphthenic acids. In addition, there were two robust summary sections for 2-ethylhexanoic acid zirconium salt.

The robust summary sections for the propionic acid metal salts indicated that they would include data for propionic acid in Appendix I; however, there was no Appendix I for this acid.

### **Followup Activity**

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.